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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 01/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,236	KLESS, HADAR	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *1-11,13-15,17,18 and 20-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,16 and 19* is/are rejected.

7)☒ Claim(s) *33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment filed October 29, 2004 is acknowledged and has been entered. Claim 33 has been added. Claims 1-33 are pending. Claims 1-11, 13-15, 17-18, 20-32 has been withdrawn from consideration as being drawn to a non-elected invention. Claims 12, 16, 19 and 33 are addressed in this Office Action. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Rejections and Objections

3. The claim rejection under 35 USC 112 first paragraph as lacking enablement is maintained and discussed below for the claim 16. The prior art rejection under 35 USC 102(b) is maintained and discussed below for the claim 12 and 19.

Claim Rejections - 35 USC § 112

4. Once again, claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of extending a nascent oligonucleotide-3'-OH in a template dependent manner, the method comprising the step of contacting the nascent oligonucleotide with a nucleic acid template, a template dependent polymerase and 1^N to 4^N oligonucleotide triphosphates each including N monomer, wherein N is an integer of 2 or 3, it does not reasonably provide enablement for a method of extending a nascent oligonucleotide-3'-OH in a template dependent manner, the method comprising the step of contacting the nascent

oligonucleotide with a nucleic acid template, a template dependent polymerase and 4^N oligonucleotide triphosphates, each including N monomers, wherein N is any integer greater than one. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)). These factors include, but are not limited to:

I. *Quantity of Experimentation Necessary:*

The claimed invention is drawn to a method of extending a nascent oligonucleotide-3'-OH in a template dependent manner, the method comprising the step of contacting the nascent oligonucleotide 3'-OH with a nucleic acid template, a template dependent polymerase and 4^N oligonucleotide triphosphates, each including N monomers, wherein N is an integer greater than 1, under conditions in which said nascent oligonucleotide-3'-OH hybridizes with said nucleic acid template and said template-dependent polymerase is active in incorporating said oligonucleotide triphosphate onto a growing 3'-OH group of the nascent olugonucleotide-3'-OH, thereby extending the nascent oligonucleotide 3'-OH in a template dependent manner. At page 18 of the specification, Applicant describes that a plurality of oligonucleotides triphosphates is provided comprising 4^N oligonucleotide triphosphates, each having N monomers in a single mix or any combination of submixes, wherein N is an integer greater than 1. The specification teaches that thus, "if N equals 2 (dinucleotide), 16 different oligonucleotide triphosphates are

included in the single mix or any combination of the submixes; if N equals 3 (trinucleotide, 64 different oligonucleotide triphosphates are included in the single mix or any combination of the sub-mixes; if N equals 4 (tetranucleotide), 256 different oligonucleotide triphosphates are included in the single mix or any combination of the sub-mixes; if N equals 5 (pentanucleotide, 1024 different oligonucleotides triphosphates are included in the single mix or any combination of the sub-mixes; whereas if N equals 6 (hexanucleotide), 4096 different oligonucleotide triphosphates are included in the single mix or any combination of the sub-mixes, and so on". Despite extensive statements in the specification referring to 4N oligonucleotide triphosphates, wherein N is any monomer greater than 1, there in no enabling disclosure as to the incorporation of oligonucleotide triphosphates onto a nascent oligonucleotide-3'OH in a template dependent manner comprising 4^N wherein N is *greater than* 2 or 3 monomers (dinucleotide or trinucleotide) as claimed. Likewise, there is no indication from the claims or specification that a oligonucleotide triphosphate comprising four or five or six or even ten or twelve monomers is capable of being incorporated by template-dependent polymerization. No information is provided that would enable one of ordinary skill in the art to make or use oligonucleotide triphosphates of any length and composition with any template-dependent polymerase without undue experimentation. Neither the Detailed Description of the invention or the Examples provided teach pertinent information concerning conditions necessary for an oligonucleotide triphosphate comprising any number of monomers to function in the method as claimed. In fact, the examples, especially Example 7 provides only a limited teaching wherein dinucleotides and trinucleotides are analyzed in a template-dependent polymerization assay. The specification discloses that "the dinucleotide is incorporated much better than the trinucleotide". However,

there is no disclosure evaluating the incorporating of a tretanucleotide or pentanucleotide or hexanucleotide or octanucleotide in any combination or etc in an extension assay as claimed. Therefore, as to the quantity of experimentation required, one of skill in the art would have to design an experimental method commensurate in scope with the instant invention.

II. *Amount of Direction and Guidance and Presence and Absence of Working Examples:*

The specification does not clearly provide any method that bears a reasonable correlation to the entire scope of the claims. The examples beginning at page 29 discloses methods of isolating five dinucleotide triphosphates (thymidylyl-3'-5'thymidine; deoxycytidylyl (3'-5')-2'-deoxyadenosine; deoxycytidylyl (3'-5')-2'-deoxycytidine; deoxyadenylyl (3'-5')-2'-deoxyguanosine; thymidylyl (3'-5')-2'-deoxycytidine) and one trinucleotide triphosphate (thymidylyl-3'-5'thymidylyl-3'-5'-thymidine). However, there is no direction or guidance given for incorporating or obtaining 4^N oligonucleotide triphosphates, each including N monomers, wherein N is any integer greater than 1, besides the dinucleotides and trinucleotide mentioned above. Therefore, further experimentation is required to one of skill in the art.

III. *Nature of the Invention*

The nature of the invention is incorporating of 4^N oligonucleotide triphosphates, each including N monomers, wherein N is an integer greater than 1. However, Applicant has only shown the incorporation of several dinucleotides and one trinucleotide. Therefore, the method of incorporating other oligonucleotide triphosphates is not reproducible due to the lack of guidance presented in the specification. As noted earlier, the specification does not properly disclose a method of making or using the claimed invention that bears a reasonable correlation to the entire scope of the claim.

IV. Relative skill of those in the art and predictability or unpredictability of the art

The level of skill in the art at the time the invention was made is very high. However, the level of unpredictability in the art is also high. For example, Moroney et al ((Biochemistry, vol. 30, No. 42, page 10438, col. 2, second full paragraph, lines 43-47) teach that "the incorporation of dinucleotide and trinucleotides into the product represents the limit of tolerance for the polymerase, and longer oligonucleotides, although complementary to the template strand, cannot be incorporated as initiating nucleotides". Likewise, the specification substantiates the level of unpredictability in the art in the teaching that dinucleotides incorporate better than the trinucleotide in the extension assay (Example 7) and lack of teaching of any other incorporation of oligonucleotide triphosphates. Therefore, for all of the foregoing reasons, undue experimentation is necessary for one of skill in the art to obtain the invention as claimed.

Applicant's Traversal

5. Applicant traverses the rejection on the following grounds: Applicant summarizes the Examiner's rejection and states that while the efficiency of incorporating oligonucleotides triphosphates having 4 or more monomers by a specific polymerase enzyme may be lower than that of shorter oligonucleotide triphosphates (as was described in Example 7), lower efficiency does not necessarily indicate inoperability or inaccuracy of a reaction. Applicant states that for example, several recent DNA polymerases enzymes used in PCR are substantially less efficient (in terms of synthesis rate and template detection) than original Taq polymerase, but are useful for their very high fidelity. Applicant states that moreover, natural polymerases involving DNA synthesis and repair in vivo posses desirable characteristics in terms of their specificity and fidelity rather than synthesis rate. Applicant states that in contrast to the Examiner's assertion,

the teaching of Moroney et al do not provide any indication as to the operability of the present invention. Applicant states that Moroney et al teach the use of di- or trinucleotides forming abortive initiation products in RNA synthesis. Applicant states that although Moroney et al teach that "....dinucleotide tetraphosphate can prime RNA synthesis but is ineffective as an elongation triphosphate", it should be noted that the present invention teaches the use of oligonucleotide triphosphates for primer extension during DNA synthesis, a process which is radically different from transcription initiation both chemically and dynamically. Applicant states that the priming of RNA-transcription requires recruitment of RNA-polymerase to a promoter region, and then synthesis of dinucleotide primers, which can be extended by additional incoming mono-nucleotide triphosphates; in contrast, the DNA primer-extension of the present invention is achieved by lining between the 3'OH of the prime, and the triphosphate group at the 5' end of the incoming building block and thus this type of synthesis should not be significantly influenced by the length of the added building block. Applicant states that therefore, the operability of incorporating an oligonucleotide triphosphate comprising four or more monomers and an initiating primer during transcription is entirely irrelevant to template dependent primer -extension using oligonucleotide triphosphate of 2 or more monomers.

Applicant states that since the incorporation of oligonucleotides having 2 or 3 monomers onto a nascent oligonucleotide has already been successfully demonstrated using a single specific polymerase, it should be well within reason to anticipate that oligonucleotide triphosphates having four or more monomers may also be successfully incorporated to a nascent oligonucleotide using a similar, or anther polymerase enzyme selected or generated capable of incorporating the large oligonucleotide triphosphates according to the teaching of the instant

application. Applicant further notes that an ordinary person skill in the art would have no difficulty synthesizing and purifying oligonucleotide triphosphates comprising four or more nucleotides using the procedure described in Example 1 and 2 of the instant application. Applicant states that an oligonucleotide of four or more monomers can be readily ordered from numerous commercial providers of custom made synthetic oligonucleotides, or by synthesis using standard methods well known in the art. Applicant states that oligonucleotide can be converted to the triphosphates form as described in Example 1, Applicant states the synthesized oligonucleotide can be purified essentially as described in the Example 1. Applicant states that the synthesized oligonucleotide triphosphates can be purified essentially as described in Example 2. Applicant further states that the instant application teaches using a variety of naturally occurring polymerases enzyme as well as engineered polymerases having an increased activity and/or specificity in incorporation oligonucleotide triphosphates onto a nascent oligonucleotide in a template dependent manner. Applicant states that this it show be well within the ability of an ordinary person skilled in the art to implement the teaching of the instant application in order to obtain, isolate or generate a polymerase enzyme capable of incorporating oligonucleotide triphosphates having 4 or more monomer onto a nascent oligonucleotide in a template dependent manner. Applicant believes that the specification of the instant application is sufficiently enabling to an ordinary person skilled in the art to make and use the method of the present invention having oligonucleotide triphosphates of 4 or more monomer as building blocks, without undue experimentation.

Examiner's Response

6. All of the arguments filed on October 29, 2004 have been thoroughly reviewed and considered but they are not found persuasive for the reasons that follow: In response to Applicant's arguments that lower efficiency does not necessarily indicate inoperability or inaccuracy of a reaction, it is noted that Applicant arguments appear to be an opinion rather factual evidence supporting such a basis. Even though Applicant cited Napolitano et al as supporting the fact that natural polymerases involving DNA synthesis and repair in vivo posses desirable characteristics in terms of their specificity and fidelity rather than synthesis rate, this evidence does not support or enables Applicant's method of extending a nascent oligonucleotide 3'-OH in a template dependent manner, comprising contacting the nascent oligonucleotide with a nucleic acid template, a template dependent polymerase and 4^N oligonucleotide triphosphates each including N monomers, wherein N is any integer greater than one. The characteristic of the polymerase does not limit the broad scope of the claims. Nor does such information support the fact that there is no disclosure anywhere in the specification that an oligonucleotide triphosphate comprising any number of monomer (e.g.,5, 10, 20, 100, 1000 monomers) is capable of being incorporated into a nascent oligonucleotide in a template-dependent manner. Likewise, no information is provided that enable one of ordinary skill in the art to make or use oligonucleotide triphosphates of any length and composition with any template-dependent polymerase, regardless of the characteristics of the polymerase. Thus the basis of Applicant's arguments does not support or enable the disclosure as claimed and without any examples or guidance in the specification, one of skill in the art would not be able to determine operability or accuracy of the invention as claimed using any number of monomers, oligonucleotides

triphosphates of any length and composition, and any template dependent polymerase in a synthesis reaction. Undue experimentation exists to practice the claimed invention. In regards to Applicant's arguments that present invention teaches the use of oligonucleotide triphosphates for primer extension during DNA synthesis, it is noted that the features upon which applicant relies (i.e. primer extension during DNA synthesis) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Likewise there is no disclosure in the claims or specification which excludes RNA synthesis or priming of RNA-transcription and thus the claimed invention as written encompasses such. In regards to Applicant's arguments concerning the Moroney et al reference as being irrelevant to the instant invention, it is noted that the citation of the Moroney reference was use to establish that unpredictability exist in the art. Likewise as note in the prior office action, Applicant specification substantiates the level of unpredictability in the art in the teaching that dinucleotides incorporate better than trinucleotides in the extension reaction (example 7). Thus one of skill in the art cannot readily anticipate the effect of change within the subject matter claimed therein. According to MPEP 2164.03, in cases where the results of change are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims (*In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). MPEP states that this is because it is not obvious from the disclosure of one species, what other species will work. In the instant invention, while it may not be difficult to obtain oligonucleotide triphosphates having 4 or more nucleotides commercially and while it may not be difficult to select a polymerase having increased activity as suggest by Applicant, it cannot clearly be

anticipated the operability and accuracy of the instant invention of extending a nascent oligonucleotide 3'-OH in a template dependent manner commensurate fully in scope as claimed. Applicant's arguments are not sufficient to overcome the enablement requirements under 35 USC 112 first paragraph.

Claim Rejections - 35 USC § 102

7. Once again, claims 12 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Moroney et al (Biochemistry, vol. 30, No. 42, pages 10343-49, 1991). Regarding claim 12, Moroney et al teach a method for extending a nascent oligonucleotide-3-OH in template dependent manner, the method comprising the step of contacting the nascent oligonucleotide-3-OH with a nucleic acid template, a template dependent polymerase and at least one oligonucleotide triphosphate under conditions in which said nascent oligonucleotide 3-OH hybridizes with said nucleic acid template and said template dependent polymerase is active in incorporating said at least one oligonucleotide triphosphate onto a growing 3' OH group of the nascent oligonucleotide-3-OH, thereby extending the nascent oligonucleotide 3'-OH in a template dependent manner (page 10347, col. 2, lines 4-10, 45-60).

Regarding claim 19, Moroney et al teach a method of extending a nascent oligonucleotide-3-OH in a template dependent manner, the method comprising the step of contacting the nascent oligonucleotide 3'-OH with a nucleic acid template, a template dependent polymerase, at least one oligonucleotide triphosphate and at least one nucleotide triphosphate, wherein said at least one oligonucleotide triphosphate and said at lest one nucleotide triphosphate are selected such that at least one monomer of said at least one oligonucleotide triphosphate is

absent from said at least one nucleotide triphosphate under conditions un which said nascent oligonucleotide 3-=OH hybridizes with said nucleic acid template and said template-dependent polymerase is active in incorporating said at least one oligonucleotide triphosphate onto a growing 3'OH of the nascent oligonucleotide 3' OH, thereby extending the nascent oligonucleotide 3'-OH in a template dependent manner (page 10347, col. 2, lines 4-10, and 45-60). Therefore, Moroney et al meet the limitations of claims 12 and 19 of the instant invention.

Applicant's Traversal

8. Applicant traverses the rejection on the following grounds: Applicant summarizes the instant claims and states that Moroney et al describes the transcription of template (Tp6) encoding the pppGAUGGC transcript with an RNA polymerase T7 in the presence of a radioactively-labeled dinucleotide triphosphates and nucleotides UTP, CTP and GTP. The reference describes the incorporation of the dinucleotide in the resulting transcript product as an initiating nucleotide. Applicant states that the teaching of the present application as recited n the claim 12 is distinct and different from the teaching of Moroney et al. Applicant states that thus while the present invention teaches extending a nascent oligonucleotide with oligonucleotides, Moroney et al., in sharp contrast, teaches initiating an RNA transcript with an oligonucleotide and extending the nascent oligonucleotide with nucleotide monomers. Applicant states that furthermore, it should be noted that Moroney et al in fact teaches away from the present invention. Applicant state that for example, in the last two lines of the Abstract, it is stated: "....a dinucleotide is not used as a substrate for subsequent chain elongation in T7 RNA polymerase catalyzed transcription reaction". Applicant states that further Moroney et al states that "with use of this template, it was established that the dinucleotide tetraphosphate could not

serve as substrate for subsequent chain elongation in T7 RNA polymerase at an "internal" position in the nascent RNA chain. Applicant states that furthermore, Moroney et al teach that the results presented here reinforce this notion in that dinucleotide tretraphosphates can prime RNA synthesis but is ineffective as elongation triphosphates. Applicant states with regards to claim 19, the arguments noted above apply herein. Applicant finally concludes that Moroney et al does not anticipate the present invention and accordingly, the claims 12, 16 and 19 are in condition for allowance.

Examiner's Response

9. All of the arguments filed on October 29, 2004 have been thoroughly reviewed and considered but they are not found persuasive for the reasons that follow: In regards to Applicant arguments that the reference of Moroney et al teaches initiating an RNA transcripts with an oligonucleotide and extending the nascent oligonucleotide with nucleotide monomers rather that a method of extending a nascent oligonucleotide with oligonucleotide with nucleotide monomers, it is noted that Applicant's specification does not exclude initiating an RNA transcript, which is an RNA oligonucleotide as being encompassed in the instant invention. In fact, Applicant's specification defines the phrase nascent oligonucleotide at the bottom of page 10 bridging top of page 11. Applicant states at line 35 of page 10, that in some cases, even a single nucleotide having a 3' OH group can serve as an initiator of nascent oligonucleotide 3'-OH. The specification continues by stating that this particularly true for some RNA dependent RNA polymerases. The specification states that page 11, line 1 that therefore, the term includes nucleic acid chains of at least one nucleotide having a hydroxyl group at its 3' end. Likewise, Applicant's claim recites that "extending" of the nascent oligonucleotide comprising

"incorporating at least one oligonucleotide onto a growing 3' OH group....". Thus, Moroney's initiating an RNA transcript by incorporating an oligonucleotide and extending the nascent oligonucleotide with nucleotide monomers is encompassed by the instant invention.

In regards to Applicant's arguments that the Moroney et al teach away from the instant invention it is noted that Applicant is only referring to one aspect of the reference of Moroney and not the entire reference as a whole. Firstly, however, the Examiner submits that the claims as written do not recite or require any subsequent chain elongation steps. In fact, the claims do not recite any "chain elongation" but rather recited "extending a nascent oligonucleotide", which based on Applicant's definition at page 10 and 11 of the specification, encompasses "incorporating even a single nucleotide having a 3'-OH group onto a nascent oligonucleotide. Nonetheless, Moroney et al teach in the abstract (lines 8 and 9) prior to the statement noted by Applicant that "incorporation of each of the theses substrates (dinucleotides) onto longer RNA transcripts in the same enzyme template system was demonstrated". Likewise, at page 10347, col. 1, beginning at the 7th line from the bottom, Moroney et al teach that giving an appropriate template sequence, incorporation of a dinucleotide tetraphosphate within the growing RNA chain may be possible. On the same page at the first paragraph of col. 2, Moroney et al disclose results obtained by testing this hypothesis and concluded that in each case, the dinucleotide was incorporated into RNA. Thus the statements Applicant is referring to do not effect the claimed invention as written because they are only based on Moroney's teaching that the dinucleoside tetraphosphate could not serve as a substrate for incorporation by T7 RNA polymerase at an "internal" position in the nascent RNA chain. The claims as broadly written do not require incorporation at any particular "position" *or* an "internal position". Thus, this teaching does not

affect the bases of the rejection set forth in the prior office action. Accordingly, Applicant's arguments are not suffcient to overcome the prior art rejections under 35 USC 102(b) and the rejections are maintained.

Conclusion

10. Claims 12, 16, 19 are rejected. Claim 33 is objected because it depends from a rejected claim. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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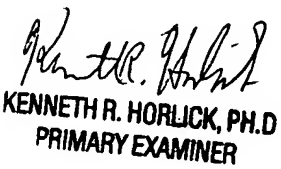

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

1/13/05